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RESEARCH IN MEDICINE ON THE PACIFIC COAST DURING 1927-1928*

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IT is generally admitted that medicine of today is so little affected by great discoveries of individual men that the historian of the twenty-first century may be at a loss to pick the greatest names from the many great ones. The art of healing is becoming the art of great masses of highly trained men. A review of the progress in medicine on the Pacific Coast is therefore an account of the achievements of the men who for the past ten or fifteen years have developed centers and schools of research. Although there are unquestionably definite tendencies in the nature of the problems under consideration by the various groups, it is evident that the West emancipates itself from the East not only in the selection of the investigative programs, but also in the skillful and frequently brilliant execution of experimental studies. In the light of the universal recognition accorded to the investigations of the Pacific Coast workers it is naturally a debatable question whether or not it is a wise procedure to herald especially the endeavors of those who might prefer to contribute to the progress of science with the least amount of notoriety and clamor. Aside from this feeling of uncertainty it must always be appreciated that in the allotted time it will be impossible to do justice to all of their research activities. This brief review obviously must be a limited and possibly a one-sided account of the achievements of a few groups of workers which, however, may serve as an inspiration to those who guide the destinies of civilization on the Coast.

For the sake of an orderly presentation the achievements may be conveniently discussed under the following group headings:

1. Research into the nature of the parasitic causes of disease.
2. Research into the nature of the causes of other than infectious diseases.
3. Fundamental investigations dealing with biological phenomena.
4. Research in the treatment of disease.

I. RESEARCH INTO THE NATURE OF THE PARASITIC CAUSES OF DISEASE

Leprosy.—Probably the most important contribution in this field has been made by Professor

Ernest L. Walker of the George Williams Hooper Foundation for Medical Research, University of California, through his bacteriological studies of leprosy extending over a number of years and continued in Hawaii during the past year. The various types of coccoid, diphtheroid and actinomycoid organisms that have been repeatedly cultivated from leprosy lesions by numerous investigators are all stages in the life cycle of one pleomorphic and facultative acid-fast organism which is a member of the genus *Actinomyces* as now constituted. Hansen's acid-fast bacterium of leprosy lesions is just one stage in the life cycle of this actinomyces. Like other thread-like forms, the lepra actinomyces is a soil organism of wide but irregular distribution. It is therefore probable that leprosy is primarily a soil infection of wounds, but this does not exclude the possibility that the disease may sometimes be transmitted by direct or indirect contact.

Tuberculosis.—In the related field of tuberculosis Dr. Frederick Ebersson, department of medicine, University of California, has continued his studies on the products of the growth of the tubercle bacillus on synthetic mediums. He has been able to isolate various fractions, some of which are thermolabile and of which others are thermostable. One of these fractions present in the Berkefeld filtrates possesses antigenic properties and behaves in many respects like a toxin. The same worker has noted that guinea-pigs treated with the toxin-like filtrate acquire a state of allergy and a specific resistance to tubercle infection. Animals injected with inactivated (heated) toxin filtrates behaved like untreated controls. The experiments of Professors C. M. Haring, J. Traum, F. M. Hayes, assisted by Mr. B. S. Henri, at the California Agricultural Experiment Station have confirmed the observation of Calmette that calves vaccinated with a strain of tubercle bacilli attenuated with cultivation on bile potato (the so-called B. C. G. vaccine = bilité Calmette-Guérin vaccine) are resistant to an intravenous injection of two milligrams of virulent tubercle bacilli. However, the protective value of the vaccination against infection by feeding milk containing tubercle bacilli has not as yet been demonstrated. The outcome of these tests will be awaited with a great deal of interest since they may help to decide the following important questions: Is the B. C. G. vaccine harmless? Does it immunize against an invasion of the tubercle bacilli by the natural portals of entry of the diges-

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tive or respiratory tract, and should it be used in the protection of infants of tuberculous parents?

By growing tubercle bacilli on media which diminished the fat and wax of the bacillus to a minimum Professor John Weinzirl of the department of bacteriology and pathology, University of Washington, was able to show that the normal bacilli and those without fat show no difference in resistance to chemical and physical agents. Apparently the assumption that the fat protects the organisms against external agents is an error.

Undulant or Malta Fever.—Undulant or Malta fever has attracted the attention of a number of workers (Dr. E. C. Dickson, Stanford University Medical School and Dr. John Ruddock, Los Angeles) since in a number of instances specific agglutinins against the bacillus of infectious abortion of cattle, *Brucella abortus*, has been demonstrated in the blood serum of patients. The old question—is the abortion bacillus or some related species pathogenic for man, and is it conveyed to human beings through raw milk—is only partially answered. Feeding experiments on monkeys by Miss B. Eddie and myself have shown that, contrary to former observations, a single feeding of several million abortion bacilli of animal and human origin regularly infect these animals. Although typical temperature reactions may be absent and blood cultures may be rarely obtained, the serum invariably contains agglutinins on the tenth to the fifteenth day after the feeding and the ingested bacilli remain latent for weeks in the spleen, bone marrow, and lymph nodes. It appears that young apes are less susceptible than older animals. Epidemiologic studies have shown that the raw milk of the dairies, which are suspected of being responsible for the human cases of undulant fever, is very heavily infected with abortion bacilli.

Tetanus.—A new type of tetanus bacillus (Type IX) found by Mr. George E. Coleman and Miss J. Gunnison in garden soil, a new type of *Cl. botulinum* (Type D) as well as a dysentery bacillus hitherto unknown in California, have been studied by members of the Hooper Foundation staff.

In contrast with all usual experimental procedures, by employing formaldehyd as a tissue debilitant, Mr. George E. Coleman has regularly infected guinea-pigs with intramuscular injections of an exceedingly small number of detoxified spores of *Cl. tetani* and *Cl. botulinum*. This dependable technique is well suited to evaluate the curative and protective properties of certain polyvalent antitoxic and antibacterial sera which have recently been prepared against these anaërobic bacteria.

Protozoan Parasites.—In parasitology Professor C. A. Kofoed of the department of zoölogy, University of California, describes a new ameba, *Councilmania dissimilis*, from human stools. This protozoa may be distinguished from *Entameba dysenteriae* by a large blob of chromatin, atypically dispersed karyosome, eight chromosomes, eight nucleated cysts and budding forms in the stools. According to Doctors H. C. Hinshaw and

F. V. Simonton of the Stomatological Research group the incidence of *Entameba gingivalis* infection in the buccal cavities of 357 individuals carefully examined was 46.34 per cent. The parasites do not occur in the strictly normal mouth. They are invariably found in typical inflammatory pyorrhea alveolaris, and they are much more frequently encountered in persons belonging to older age groups. Although the etiological relationship of these protozoa to parodontoclasia is by no means clear it is noteworthy that Professor C. A. Kofoed and Doctor Hinshaw have demonstrated the distribution of the *Entameba* in the pyorrheal pocket. A peculiar biological association of *Leptotrichia*, calculus and ameba produces a very interesting picture. The *Leptotrichia* are directly concerned with the deposition of calcium salts. In the masses of the projecting filaments the conditions favorable for shelter, food supply, and reaction encourage the multiplication of the ameba, while in turn the inflammatory process in the interdental papillae supplies the nuclear detritus which may be required by the protozoa and may also contribute to the phosphatic material of the calculus. Doctor Hinshaw has also successfully infected dogs with *Entameba gingivalis* and *Trichomonas buccalis* of the human mouth. The infection persisted for four months, and was only successful when inflammatory and gingival pocket formation existed prior to the beginning of the experiment.

Quantitative examinations of the mouth flora under different dietary conditions by Miss B. F. Howitt of the Hooper Foundation and Dr. W. C. Fleming of the Stomatological Research group have shown that the oral bacteria are more influenced by the local food remains than by any general systemic effect produced by dietary changes. Artificial cleaning with the toothbrush is many times more effective in reducing the absolute number of mouth organisms than is the supposed cleansing accomplished through a diet composed presumably of detergent elements.

Bacterial Toxin Production.—The mechanism of toxin production of certain bacteria and the chemical nature of the poisons are still unknown although Dr. Claus W. Jungeblut of the department of bacteriology and experimental pathology, Stanford University, has confirmed previous observations that toxic and virulent strains of *B. diphtheriae* may be dissociated into atoxic varieties by means of cultivation in a medium containing specific antitoxin. However, these altered strains retained their virulence for guinea-pigs. Furthermore the atoxic filtrates gave definite flocculation with diphtheria antitoxic sera according to the method of Ramon. Miss E. Lewis of the department of bacteriology, University of California, has made similar observations on the toxin and antitoxin mixtures of *Cl. botulinum*. These various results cast considerable doubt on the specific nature of the flocculations which occur in neutral mixtures of bacterial toxins with their respective antitoxins. Some progress has been made in the purification of the botulinus toxin. Dr. H. Sommer and his associates at the Hooper

Foundation have secured highly potent dry toxins by adjusting a toxic filtrate to a P_H of 4.4 and by dialyzing the precipitate. Such toxins are remarkably stable and their pharmacologic properties, contrary to the views of Bronfenbrenner are not intensified by acidification. Furthermore the potency of the poison according to Mrs. Wagner-Sommer can be enhanced by a brief incubation with protein solutions previous to the subcutaneous inoculation.

A new principle, a nonspecific systemic adsorption for a rational chemotherapy of bacterial intoxications, has been developed by Dr. P. J. Hanzlik, professor of pharmacology, and Dr. E. M. Bilt, assistant in pharmacology, Stanford University School of Medicine. The protective action of twenty-three dyes and drugs was tested in mixtures with botulinus, diphtheria and tetanus toxins injected locally, and also by injection of the dyes intravenously and the toxins intramuscularly. Of all the agents tried Congo red was most efficient. Intravenous injection of the dye protected the majority (about 80 per cent) of the animals poisoned with diphtheria and botulinus toxins, but not those poisoned with tetanus. Congo red protects also against poisoning from a variety of drugs (curare, strychnin, guanidin, oxalates, morphin). Since a physical binding of the curare occurs in curare-congo mixtures it is suspected that the same is the case with the toxins. In fact all the evidence indicates that the mechanism of the protection is mediated through the physical properties of the dyes, *i. e.*, through surface activity in which adsorption is the dominant factor.

Bacteriophage Phenomena.—Professor E. W. Schultz has diligently pursued his investigations on the bacteriophage phenomena. Contrary to the general belief that bacteriophages active against intestinal organisms exhibit a high degree of resistance to the action of trypsin, he found two races of staphylococcus lysin rendered inactive by this ferment within a period of about forty-eight hours. In collaboration with Mr. K. M. Taylor he secured a lytic filtrate from eight spontaneous tumors of white mice active against the dysentery bacillus. It is conceivable that the bacteriophage in these tumors originates from the intestinal content of the mice.

Local or Tissue Immunity.—Various factors are probably responsible for the many manifestations of local or tissue immunity which have been studied in recent years. Dr. H. L. Averill at the Hooper Foundation was able, contrary to previous knowledge, to protect guinea-pigs against a fatal infection with aertrycke bacilli through the skin, provided that twenty-four to forty-eight hours prior to the injection of the virulent organism the skin had been treated with "antivirus." The same principle, according to Mr. L. Hertert, Hooper Foundation, does not afford immunity against a hemolytic skin-invasive streptococcus of guinea-pig origin. However, the Besredka method of local treatment with specific dressings, in the light of encouraging clinical results reported by Dr. H. L. Averill, deserves more extensive investiga-

tions. Dr. Rachel E. Hoffstadt, department of bacteriology and pathology, University of Washington, has vaccinated groups of students by mouth. Triple typhoid vaccine in gelatin capsules containing an alcoholic extract of bile in a starch matrix were administered orally before breakfast. Since agglutinins and other antibodies appeared in the blood it is evident that a general immunity response and not a local tissue resistance was induced by the oral vaccination. A local mechanism of defense in the uterus during the puerperium is suggested from experiments of Dr. C. F. Fluhmann, division of obstetrics and gynecology, Stanford University School of Medicine. During pregnancy the reticulo-endothelial cells tremendously increase both in number and in activity in the pars uterinae, the cornu and the tubes of rabbits. This behavior of the cells persists for several weeks during the puerperium.

2. RESEARCH INTO THE NATURE OF THE CAUSES OF OTHER THAN INFECTIOUS DISEASES

In this group will be considered a variety of studies on dietary deficiencies, the function of endocrines, heredity and general physiology.

Antisterility Vitamin Fat-Soluble E and Other Vitamins.—First in importance are the researches of Professor H. M. Evans, Dr. George O. Burr, and their associates in the department of anatomy, University of California. Their extensive studies on the antisterility vitamin fat-soluble E have been summarized in a valuable monograph. More recently during the same investigation it was found that the curative effect of the fertility vitamin E, present in wheat germ, is counteracted by certain substances in fats and oils. Furthermore they have observed that highly purified and almost fat-free diets which give subnormal growth and ovulation, except when supplemented with small amounts of beef liver, lettuce or lard, can also be adequately supplemented by other fats, in particular by coconut oil, corn oil or butter. It is not unlikely that the favorable substance, since it can be recognized only in the fatty acid portion after saponification of the fats, is a new vitamin (F).

Diets and Growth.—In another series of experiments the same workers have noted that a "pure" diet of casein (Van Slyke), sucrose and salts is not adequate for normal growth even when supplemented by very high levels of vitamins A, B, C, D and E. Lactation fails with the pure diet. The inclusion of lettuce or lard in the diet allows the females to produce good litters and they successfully wean them, but the second generation is always retarded in growth. These observations suggest that the "pure" diet requires either an extraordinary amount of some of the known vitamins or an unknown member (F or H) of the vitamin class.

Lactation and Vitamins.—That successful lactation demands more growth-promoting vitamin B than normal growth of the mother has been stressed by pediatricists and experimenters on dietary deficiencies. According to Professor C. U.

Moore and his associates at the Collin's Nutritional Research Laboratory, University of Oregon Medical School, additional proof has been furnished that young rats nursed by mothers on a minimum vitamin B diet show a high mortality from polyneuritis and visceral and cerebral hemorrhages. By increasing the yeast in the diet from 2 to 7 per cent the mortality may be decreased from 72.9 to 9.3 per cent. Similar experiments of Professor Evans and Doctor Burr clearly indicate that the additional yeast is needed for lactation solely because of its contribution of anti-neuritic vitamin B and not because of the growth-promoting vitamin B of the diet. The following observation confirms this. When tikitiki (a dilute alcoholic extract of white rice polishings made by the Philippine Bureau of Science), which is almost lacking in growth-promoting vitamin B, is given to lactating mothers without increased yeast dosage normal lactation can also be produced. Clinical observations by Dr. C. U. Moore of Portland leave no doubt that the laboratory findings have a direct bearing on the problem of the nutritional requirements of lactating women, who on the average American dietary produce a milk that is exceedingly low in vitamin B. Equally important are the experiments of the same worker, who was able to show that puppies were stunted and prematurely died when vegetable fats were substituted for butter in the diet. An excess of alkali in the diet, regardless of its calcium-phosphorus ratio may, according to Doctors M. R. Jones and F. V. Simonton of the Stomatological Research group, initiate retrograde skeletal and dental defects comparable to those seen in man. The alveolar process appears to be more susceptible to slight dietary errors than do the long bones. In fact, diets which are potentially basic in reaction and low in calcium, protein and vitamins produce in adult dogs lesions similar to those of a noninflammatory type of parodontoclasia which may be cured by feeding hydrochloric acid and cod-liver oil, in conjunction with roentgen rays. The studies of Mr. Ohman Horace Cady of the department of chemistry, Stanford University, suggest that vitamin A is withdrawn from the blood as rapidly as absorbed from the alimentary canal of dogs. The concentration of this vitamin in the blood of dogs is normally very low, and it undergoes no measurable increase during the absorption of large amounts from the digestive tract.

Avitaminoses.—The general organ and tissue injuries which develop in the course of certain avitaminoses deserve a more careful study than has hitherto been made. It is therefore most gratifying to note that a number of workers have addressed themselves to this difficult and not always appreciated task. Professor A. W. Meyer and Mr. L. M. McCormick of the department of anatomy at Stanford have made a careful gross and microscopic study of the tissue changes in experimental scurvy of guinea-pigs. An almost universal afebrile, lytic process induces frequently hemorrhages because of the destruction of the walls of the blood vessels, necroses, degenera-

tions in the parenchymatous organs, anemia and changes in the skeletal system, etc. The changes in the gums and teeth produced in rats on deficient diets have been analyzed by Dr. J. A. Marshall of the College of Dentistry, University of California. Dr. K. S. Bishop of the Hooper Foundation, working under the auspices of the John C. and Edward Coleman Fund, noted marked abnormalities of the skull bones and bones of the ear capsule, including the stapes and other ossicles, produced by two ricket diets. However, this is a completely generalized abnormality in both instances, and these diets do not cause localized areas of distorted tissue. Furthermore, the ligament of the foot plate of the stapes and the articulating cartilage cells remain unaffected.

Paralysis and Deficient Vitamins.—An upper motor neurone paralysis induced in rats by vitamin-E deficient diets is the subject of a careful inquiry by Professor H. M. Evans, Doctors Burr and R. W. Harvey of the department of anatomy, University of California. Finally, vitamin A injures the female reproductive system of the rat so that fertilization and implantation fail (Professor Evans) or spontaneous deciduomatous tumors develop in the uterine horns of rats kept on diets low in vitamin A (Doctor Bishop) or E (Professor Evans and also Doctor Bishop and Professor Agnes F. Morgan).

Diabetes.—A year ago Bergey of Philadelphia announced that diabetes mellitus could be produced in rabbits by a single intravenous injection of a sterile Berkefeld filtrate of the urine of diabetic patients. Professor E. W. Schultz and Messrs. S. J. Johnson and G. T. Akaimatsau of the department of bacteriology and experimental pathology, Stanford University, in carefully controlled experiments were unable to confirm these observations.

Mussel Poisoning.—A catastrophic and extensive outbreak of mussel poisoning, which occurred in July, 1927, in the vicinity of San Francisco, prompted Dr. H. Sommer, Miss P. Schoenholz and myself to make an inquiry into the nature and the origin of the poison. It was found that fresh *Mytilus californianus* collected on the coast contain a highly potent nerve poison, probably a quarterly or tertiary amin, which is readily extracted with alcohol or acidified distilled water. The poisonous properties have disappeared during the winter months, but have again appeared in certain mussel beds as far north as Eureka. A metabolism disease of the mollusks intimately associated with the spawning functions is suspected.

Rattlesnake Venom.—Special methods of collecting rattlesnake venom for the preparation of a potent antivenin have been developed by Dr. L. M. Klauber of the Zoölogical Society of San Diego.

Pituitary Gland.—During the past ten years the mystery surrounding the physiology of the pituitary gland has been gradually unveiled by workers on the Pacific Coast. That the anterior hypophysis is indispensable for growth and that an increased amount of the hormone of this organ

is the direct cause of overgrowth, is now fully established. It is equally certain that a lessened amount is the cause of various endocrine dystrophies. Professors Philip E. Smith and Earl T. Engle of the department of anatomy, Stanford University, working on hypophysectomized rats, were able to overcome the disabilities produced by the removal of the pituitary by fresh daily homo- and heterotransplants of the hypophysis. Professor F. L. Reichert of the department of surgery, Stanford University Medical School, has obtained similar results by this replacement therapy, using rabbits' hypophyses on a puppy whose pituitary was removed when six weeks old.

Hypophysis and Sex Gland Function.—The relationship of the hypophysis to the normal function of the sex glands is evidenced by several recent studies. Professors Philip E. Smith and Earl T. Engle have observed that the administration of a gonad-stimulating substance, probably a hormone, from the anterior hypophysis liberates in rats, mice and guinea-pigs a large number of ova. These eggs may be fertilized and as many as twenty-nine embryos may develop in a single pregnancy within a month. According to Professor Engle the same hormone is the regulatory factor in compensatory ovarian hypertrophy, thus an increased amount causes ovarian grafts to develop mature and cystic follicles, even when transplanted into the testis of an adult male. According to Dr. G. Van Wagenen of the department of anatomy, University of California, the hypophyseal extract raises the body length and the weight of castrated male rats above that of the controls. Large placentomata may develop if, according to Dr. L. Brouha of the same department, rats are injected daily with hypophyseal fluid and if the uterine mucosa is injured around the fifth day of injection and the animal killed five to seven days after operation.

Hereditary Transmission.—Constitutional or hereditary factors unquestionably play an important rôle in the etiology of certain diseases. For a number of years Professor C. H. Danforth of the department of anatomy, Stanford University, has followed in laboratory animals the hereditary transmission of such conditions as adiposity, anemia, the doubling and reduction of parts in the mouse, and the abnormal persistence of caudal endoderm. More recently he has, in collaboration with Mr. Francis Foster, studied the agents regulating plumage production and the relation of certain genetic and endocrine factors to somatic manifestations in the fowl. Through skin grafting a convenient method has been found of analyzing some of the factors involved in feather production and in growth changes in the developing skin. The experiments indicate that several similar, if not identical, feather characters can be produced either by breeding or by therapy. Dr. E. S. Sundstroem of the department of biochemistry, University of California, has concluded experiments of several years' duration on the effects of climatic environment, with special reference to temperature and humidity upon the growth and metabolic activities of the rat. The work was

undertaken to check in a more precise way his previous reported work on the effects of tropical climate on the behavior of man.

Cholesterol.—In an experimental study Professors F. E. Blaisdell and Dr. L. R. Chandler of the Laboratory of Surgical Research, Stanford University Medical School, have found that a continued hypercholesteremia in the rabbit and dog results in deposits of cholesterol containing fat in the mucosa and submucosa of the gall bladder provided the cystic duct is patent. Since the deposits of cholesterol in the wall of the gall bladder are dependent upon the absorption of this substance from the bile no cholesterol-containing fat was found when the cystic duct was ligated.

Hemochromatosis.—Hemochromatosis, a disease in which an extraordinary deposition of iron containing pigment together with other pigments is found in practically all organs including the skin, remained until recently an unsolved problem. Professor E. M. Hall and Mr. E. M. Butt of the department of pathology, Stanford University Medical School, in confirming the work of Mallory, have produced in the liver a condition in many respects similar to that observed in human hemochromatosis by poisoning rabbits with copper. Observations of Doctors T. L. Althausen and William J. Kerr of the department of medicine, University of California Medical School, suggest that this disturbance of the pigment metabolism may be restored to normal with insulin.

Cancer Study.—The organization of a cancer division at the Pasadena Hospital under the direction of the well-known investigator, Dr. Montrose T. Burrows, formerly of the Barnard Free Skin and Cancer Hospital, St. Louis, promises great developments in research into the causes and treatment of malignant tumors. Cancer which is not a disease of itself is probably only one type of change which the body suffers in the abnormal aging of its parts. Doctor Burrows has shown that it can be induced by producing hyperfunction of any organ. Furthermore, experimental studies dealing with the relationship between infection and cancer have shown that cancer stands at one end of the scale and infection at the other.

3. FUNDAMENTAL INVESTIGATIONS DEALING WITH BIOLOGICAL PHENOMENA

Without a thorough knowledge of the mechanisms of biological phenomena the many problems in medicine cannot be solved. It is therefore not surprising that the medical institutions of today participate more and more in the elucidation of general physiological and biochemical phenomena as observed in the animal kingdom. It is this group of studies which deserves some consideration.

Allergy.—Hypersensitiveness or allergy offers many fascinating problems. Professor W. H. Manwaring and his associates, Messrs. J. L. Azevedo and H. C. Torbert of the department of bacteriology and experimental pathology, Stanford University, report on experiments with Maignon's fraction of anaphylactic blood. They were able to confirm the findings of this investigator that the acquired hypersensitiveness in dogs

may be transmitted by the proteose-peptone-amino-acid fraction of anaphylactic blood. However, the symptomatology and autopsy findings are not those of typical anaphylaxis. Maignon's product when used by special experimental methods probably induces not a true passive anaphylaxis but some atypical phenomenon of hypersensitiveness. Professor Manwaring has also observed that horse proteins injected intravenously into normal dogs are so completely denatured by the end of four days as to lose their original antigenic properties. Contrary to expectations from current immunological theory, the denaturization is slower in immune dogs, rarely being complete before the sixth day.

Anaphylactic Shock.—Messrs. F. R. Van de Carr and O. B. Williams of the department of bacteriology, University of California, have extended their previous observations on the influence of heparin on the anaphylactic shock in the guinea-pig. Again, it was found that when heparin is injected into the circulation in an amount sufficient to prevent during twenty-four to forty-eight hours or longer the formation of a blood-clot, the anaphylactic syndrome, determined by very sensitive methods, was prevented in 60 per cent of the sensitized guinea-pigs if the dose was injected previous to the application of the shocking dose. Furthermore, the inhibitive action of heparin can be removed if the colloidal balance of the blood has been disturbed by a previous injection of heterophile antigens or 2 per cent sodium citrate solution. This observation suggests that in the guinea-pig the cause of the anaphylactic symptoms is probably governed by physicochemical disturbances in the colloidal balance of the blood leading to a coarser dispersion. The same explanation may apply to the experiments of Professor Claus W. Jungeblut of the department of bacteriology and experimental pathology, Stanford University, which showed that the intravenous injection of 0.02 gram of neoarsphenamin into actively and passively sensitized guinea-pigs, if given fifteen to twenty minutes before the reintroduction of the specific antigen, was capable of saving approximately 50 per cent of the animals from fatal anaphylactic shock.

Tuberculin Reaction.—According to Messrs. F. R. Van de Carr and William R. Lyons of the departments of bacteriology and anatomy, University of California, "Tutocain," a trade name for the hydrochlorid of p-amino-benzoyl-di-methyl-amino-methyl-butanol, protects tuberculous guinea-pigs against a fatal dose of tuberculin, provided the local anesthetic is injected at least thirty minutes prior to the application of the tuberculin. It is not unlikely that the local edema favors a gradual but progressive desensitization and thus protects the animals from a fatal reaction. Intimately related to these phenomena are the studies by Dr. S. H. Hurwitz of the department of medicine, Stanford University, and Miss P. Schoenholz of the Hooper Foundation on the mechanism of passive transfer of human hypersensitiveness, bacterial allergy and the mechanism of skin tests in hay fever and asthma as well as

those by Doctors Robert W. Lamson and Gordon Alles of the Allergy Clinic of Dr. George Piness at Los Angeles on the specificity of the intracutaneous pollen test in man.

Compensatory Hypertrophy.—For a number of years Doctors T. Addis, L. L. and E. M. Mackay of the department of medicine, Stanford University Medical School, have made a study of the factors involved in the process of "compensatory hypertrophy." In the albino rat, after the removal of one lung the remaining lung showed an average increase of more than 40 per cent, while the removal of one adrenal gland is followed by hypertrophy of the cortex of the remaining gland. Preliminary to a systematic investigation of the well-known hypertrophy of the remaining kidney following unilateral nephrectomy by new methods the same workers have collected important observations on the influence of such factors as age, sex, food variations (protein, sodium, phosphate), etc., on the kidney weight. In the course of these studies the important fact has been established that in the rat the kidney weight-body surface ratio is constant at all ages while the kidney weight-body weight and the kidney weight-body length ratios vary at different ages. Furthermore, sex, like age, determines the renal weight; the female rat has less renal tissue per unit of body size than the male rat.

Recovery Oxidation After Muscular Exercise—Pregnancy Demands.—Contrary to the hypothesis of A. V. Hill, Professor E. G. Martin and Doctors Field and Hall of the department of physiology, Stanford University, have found that the recovery oxidation following muscular exercise cannot be attributed to a specific dynamic action of the increased blood lactates. Some other explanation for the recovery phenomenon must be sought, since high concentrations of blood lactates induced by physiological means were either not attended by any increase in oxygen consumption or the increase was slighter and less persistent than in typical examples of recovery oxidation in which blood-lactate concentration was no greater. Professor J. R. Slonaker of the department of physiology, Stanford University, reports that rats, virgin throughout life, show much more voluntary activity than rats bearing young, even though the latter were relieved of caring for and nursing the young after birth. Breeding rats consume more food than virgins, thus showing that the energy requirements of periods of childbearing exceed those of equivalent periods of voluntary bodily activity.

Sympathetic Function in the Esophagus.—The dual origin, from the superior cervical and thoracic ganglia, of the sympathetic function in the esophagus of pigeons has been studied for the first time by Professor P. J. Hanzlik and Dr. E. M. Butt of the department of pharmacology in the Stanford University Medical School. Striking and interesting responses to many drugs have been noted; for example, the contracted esophageal muscle can be relaxed or reversed by drugs and conditions physically and chemically different and which of themselves cause contraction. How-

ever, the same drug or stimulus cannot oppose its own action. For the relief of esophageal spasms epinephrin is therapeutically indicated.

Spinal Cord Pathways—Eye Innervation.—A number of other reports on neurological studies should be mentioned, but they cannot be briefly summarized. Professor W. F. Allen, department of anatomy, University of Oregon Medical School, has located in the spinal cord the pathways by which are conducted impulses from the cerebrum and superior colliculus and which affect respiration. Professor O. Larsell of the same department analyzed the innervation of the pleura pulmonalis; Messrs. O. L. Huddleston and H. E. de Feo of the department of physiology, University of California, investigated the reciprocal innervation of antagonistic eye muscles of dogfish; and Professor F. W. Weymouth explored the foveal region of the retina in respect to visual acuity in order to throw light on the mechanism of control of eye movements.

Biochemical Studies—Amino-Acids; Calcium Fractions; Calcium Phosphorus Magnesium.—Biochemical studies by Professor J. M. Luck of the department of chemistry, Stanford University, with the aid of a new method indicates that the oral administration of amino-acids to rats causes increases of varying magnitude in the amino-acid content of the liver, but no appreciable change, except in the case of glycine, in the amino-acid content of the muscle. Furthermore, since the administration of insulin to normal animals induces a lowering in the amino-acid content of the blood, liver, etc., it is suspected that insulin hypoglycemia induces a compensatory increase in the rate of glucogenesis from amino-acids. Professor C. L. A. Schmidt and his associates, Drs. D. M. Greenberg and Kirk of the department of biochemistry, University of California, have shown that sodium and barium salts of certain amino-acids behave as strong electrolytes. This is also true for sodium caseinate. Barium caseinate, on the contrary, is abnormal in its behavior, indicating therefore the presence in such solutions of complex ions. The same workers have determined the dissociation constants of serine, valine, isoleucine, and oxyproline. According to Dr. D. M. Greenberg and Mr. H. E. Ballard of the same department the diffusible and nondiffusible calcium fractions in various pathological sera may vary, but the spinal fluid calcium remains constant. This seemingly indicates that spinal fluid calcium does not represent a true diffusate. Professor Schmidt and Mr. H. Goss are studying the calcium, phosphorus and magnesium metabolism in rats during the period of pregnancy and lactation. A storage of calcium begins immediately after the onset of pregnancy and in amounts which indicate that adequate provision is not only made for the fetus, but also in anticipation of the period of lactation at which time there is a very heavy demand upon the body for calcium and phosphorus.

Oxidation-Reduction Potentials.—Professor J. P. Baumberger of the department of physiology at Stanford University has developed an

electrometric method which promises to be of importance as an aid in determining the oxidation-reduction potentials of the irreversible reactions by which energy is liberated in living tissues.

Insulin Substitutes.—Synthalin and glukorment, substitutes for insulin recommended by European workers, are, according to Doctors N. R. Blatherwick and F. Bischoff of the Santa Barbara Cottage Hospital, useless in the treatment of diabetes. The lowering of the blood sugar and the sugar in the urine, incident to taking these drugs, is probably due to liver damage which prevents the change of protein into sugar rather than the burning of sugar itself.

4. RESEARCH IN THE TREATMENT OF DISEASE

Observation and experiment in the treatment of disease form a great and essential part in medical research. Only a few of the achievements can be mentioned.

Buccal Infections.—A troublesome infection of the buccal cavity transmitted by dust and occasionally occurring in epidemic form among newborn infants, according to Dr. Harold K. Faber and Dr. E. B. Clark of the department of pediatrics, Stanford University School of Medicine, can be effectively cured by an application of gentian violet.

Bismuth and Syphilis.—In search for effective antisyphilitic remedies, Doctors H. G. Mehrtens and P. J. Hanzlik, professor of medicine and pharmacology respectively, and Messrs. D. C. Marshall and N. S. Brown have adopted a program of clinical and experimental studies with bismuth and its compounds. Regardless of the preparation used, bismuth injected intramuscularly in man is absorbed and a portion excreted through the kidneys, but a considerable amount which is stored in the body can be mobilized in the blood stream by hot baths and vaccines. No evidences of toxicity from metallic bismuth have been encountered among one hundred individuals receiving a total of 1500 injections irrespective of the considerable amount of bismuth which may be stored in the body.

Balantidium Coli Infections.—Spontaneous *Balantidium coli* infections of guinea-pigs may, according to Miss M. Sweeney of the Hooper Foundation, in a high percentage of instances be cured with tryparsamid and stovarsol. The latter preparation has also been successfully employed by Dr. H. E. Butka, associate professor of pathology, College of Medical Evangelists, Los Angeles, in the treatment of a group of medical students infested with protozoan parasites.

Cancer—Low Protein Diets—Liver Treatment—Subcutaneous Blood Transfusions.—Promising results in the treatment of cancer are reported by Doctors H. J. Ullmann, N. R. Blatherwick and F. Bischoff of the Santa Barbara Hospital with a colloidal lead phosphate of low toxicity. Dr. W. D. Sansum of the same institution has discovered that the elimination of fat from the diabetic diet and the use of high carbohydrate diets in the treatment of diabetes are just as

important as the use of insulin. According to Doctors F. R. Nuzum and Sansum the use of diets low in protein has in over one thousand cases resulted in a reduction of the abnormally high blood pressure and a marked improvement in all with the exception of a very few whose blood vessels and kidneys were damaged beyond repair. Professor A. L. Bloomfield of the department of medicine, Stanford University Medical School, has successfully treated cases of sprue with raw liver and with the Minot-Murphy liver extract, which is now generally employed in the cure of pernicious anemia. In this connection it is of interest to note that Doctors William J. Kerr and E. H. Falconer of the University of California Hospital have observed a patient with a very marked anemia, due to *Dibothriocephalus latus* to respond to the liver treatment. This is probably the first evidence of the action of the liver extract on this type of anemia. Since Professor O. Larsell and Doctors N. W. Jones, B. I. Phillips and H. T. Nokes of the University of Oregon Medical School have observed that injected nuclei of red blood cells and nucleic acid stimulate the blood-forming organs, they conclude that the nucleoprotein, and not a special hormone, is the active substance of the beef liver. Subcutaneous blood transfusions, according to Dr. C. M. Moore of the Collin's Nutritional Research Laboratory, University of Oregon Medical School, are just as effective as intravenous transfusion and, since the dangers of hemolysis and agglutination are eliminated, the method is safe and deserves more universal use.

Surgery in Tuberculous Abscesses.—In surgery Professor E. Holman, department of surgery, Stanford University Medical School, has demonstrated on dogs that by the use of an atraumatic technique of closing the bronchus, lung lobes containing tuberculous abscesses may be removed successfully.

Salicylates—Ephedrin Substitute.—Doctors C. C. Johnson and P. J. Hanzlik and Mr. M. A. Seidenfeld, department of pharmacology, Stanford University Medical School, have investigated the pharmacology of ammonium salicylate and synthetic salicyluric acid. The ammonium salicylate possesses more marked diuretic and metabolic effects with no greater toxicity than other salicylates. However, its fate in the body is different owing to the destruction of the ammonium ion. Salicyluric acid, a conjugation product of salicyl and glycocoll, is relatively inert. Phenylethanolamin, a substitute for ephedrin, recently synthesized by Dr. Gordon Alles in the clinic of Dr. George Piness of Los Angeles, resembles in its action tyramin and ephedrin. According to Dr. W. L. Tainter, department of pharmacology, Stanford University Medical School, it is an effective drug in causing shrinkage of the turbinates and nasal mucosa. In the treatment of bronchial spasm it is less effective, but as a depressor agent it has more desirable qualities than epinephrin and ephedrin.

Morphin Substitute.—According to Dr. F. W. Lynch, department of gynecology and obstetrics,

"Allonal" = Allyl-isopropyl-barbituric acid-amino pyrin is an excellent substitute for morphin in postoperative therapy. This drug when given for a period of two or three days reduces the incidence of postoperative vomiting and almost entirely eliminates abdominal distention following operations.

Comment.—As already stated in the introduction this report is incomplete, but it gives an outline of the progress which has been made in research in medicine on the Pacific Coast during the year 1927-1928.

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THE RADICULAR SYNDROME IN HYPERTROPHIC OSTEOARTHRITIS OF THE SPINE*

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DISCUSSION by James F. Churchill, M. D., San Diego; Milton B. Lennon, M. D., San Francisco; Howard H. Markel, M. D., San Francisco; John Homer Woolsey, M. D., San Francisco.

SINCE von Bechterew's¹ original description of stiff spine associated with neurological symptoms and nerve root degeneration, much discussion has ensued regarding the classification of the various forms of spondylitis, and the neurological side of the syndrome has received inadequate attention.^{2,3} The finding of nerve root degeneration by Rhein⁴ in a case of *Spondylose rhizomelique* indicates that the neurological pathology is essentially alike in the various types of spondylitis and from the very nature of the process, nerve root symptoms should be present in the P. Marie and Strümpell, as well as in the Bechterew type. The experimental work of Nathan⁵ lends further weight to this view and indicates that the various forms of spondylitis are merely accidents of localization of a process which is generalized. Subjective and objective disturbances should be present in all types.

DEFINITION OF RADICULITIS

Dejerine⁶ described radiculitis as an acute inflammation of the spinal roots, manifested by alterations of sensation or of muscle function which show by their distribution that the primary disease process producing them is in the spinal root (Fig. 1) and not in the tracts and nuclei of the cord or in a peripheral nerve trunk. The neurological syndrome described by Bechterew received little consideration, however, until the work of Sicard⁷ on funiculitis and neurodocitis which associated osteoarthritis of the spine with the radicular syndrome. There are no criteria by which the neurodocitis or funiculitis of Sicard (extrameningeal involvement of the roots) can be distinguished from involvement of the intra-

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